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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/925,620 | 08/10/2001 | Shirley I. Miekka | CI-0002 | 2935 |

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| EXAMINER | |
|---|---|
| MCKANE, ELIZABETH L | |
| **ART UNIT** | **PAPER NUMBER** |
| 1744 | |

DATE MAILED: 05/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/925,620 | MIEKKA ET AL. | |
| | Examiner | Art Unit | |
| | Leigh McKane | 1744 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 February 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *81-263* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *131-148 and 204-228* is/are allowed.

6)☒ Claim(s) *81-128,149-203 and 229-263* is/are rejected.

7)☒ Claim(s) *129 and 130* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

### *Claim Rejections - 35 USC § 102*

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 85-87 are rejected under 35 U.S.C. 102(b) as being anticipated by Wiesehahn et al (U.S. Patent No. 4,727,027).

Wiesehahn et al teaches a method for sterilizing biological materials with UV radiation at a controlled rate and for a time sufficient to sterilize the material. See col.4, lines 20-40. A sensitizer and/or oxygen scavenger may be added to the material before irradiation and preferably the material is irradiated at a temperature below 60 °C, most preferably -10 to 30 °C. A ligand stabilizer (heparin) is added to control any activated clotting factors (col.11, lines 31-33).

### *Claim Rejections - 35 USC § 103*

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 81-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horowitz et al (U.S. Patent No. 5,712,086) in view of either Salim-Hanna et al (Abstract of "Free radical scavenging activity of carnosine") or Gottlieb et al (U.S. Patent No. 5,912,241).

Horowitz et al teaches a method of radiation sterilizing sensitive biological materials combined with stabilizer mixtures and sensitizers. See Abstract. The stabilizer can be ascorbate in mixture with another stabilizer. See Table IX. Horowitz et al discloses exposing the materials to particular fluences of radiation (col6, lines 57-62) for particular time periods (col.7, lines 45-48) and the materials may be in a frozen state (col.7, lines 47-48). Radiation sources include UV, gamma, x-rays, and visible light. See col.6, lines 48-56. Horowitz et al does not teach use of a dipeptide stabilizer or a mixture of ascorbic acid with 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid.

Salim-Hanna et al teaches that the addition of carnosine, a dipeptide stabilizer, to peroxidase and lysozyme prior to irradiation, prevents free radical damage thereto. Therefore, it would have been obvious to add carnosine to the biological products of Horowitz et al prior to irradiation in order to prevent free radical damage.

Alternately, Gottlieb et al discloses that it was known in the art at the time of the invention to employ quenchers such as mannitol, glutathione, vitamin E, and Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid), alone or in combination, in radiation treatment of biological products. See col.6, lines 35-41. As Horowitz et al already teaches the use of mannitol, glutathione, and vitamins such as ascorbate and vitamin E (α-tocopherol), alone and in combination, it would have been obvious to use Trolox as well, since Gottlieb et al illustrates that it is a functional equivalent of the quenchers used by Horowitz et al.

5. Claim 84 is rejected under 35 U.S.C. 103(a) as being anticipated by Horowitz et al in view of either Salim-Hann et al or Gottlieb et al as applied to claim 84 above, and further in view of Peterson (U.S. Patent No. 5,730,933).

The above combination fails to teach both reducing the residual solvent of the biological material and reducing the temperature of the material. Peterson teaches sterilizing a biological material wherein the material is lyophilized, treated with a free-radical scavenger or antioxidant, stored in a vacuum with an inert gas at -70°C, and irradiated with gamma radiation. See col.5, line 8 to col.6, line 18.

As the combination of freezing and lyophilization reduces the number of hydroxyl radicals available for reaction with the biological material, it would have been obvious to do both in the method of Horowitz et al.

6. Claims 85-90, 100-116, 125-127, 229-233, 241, 242, 246, 248, and 254 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson in view of Horowitz et al and Wiesehahn et al (U.S. Patent No. 4,727,027).

Peterson teaches the use of e-beam or gamma radiation to sterilize a biological material (e.g. whole blood, collagen, recombinant proteins, peptides) that is sensitive to radiation, wherein a stabilizer (antioxidant/free-radical scavenger, such as ascorbate or propyl galate) is added to the material prior to irradiation and the material is then irradiated within a package "under standard sterilization conditions...at an intensity and for a time duration sufficient to destroy substantially all of the microorganism contamination" (col.4, lines 59-64). See also col.4, lines 36-51; col.6, lines 1-18. The material may also be lyophilized or dried with drying agents and/or frozen and placed under a vacuum or inert gas, such as nitrogen or argon (col.4, lines 51-58; col.5, lines 28-35 and lines 53-67) and/or stored at -70°C. The sterilized tissue may be used to treat a disease or deficiency and retains about 50% to about 100% of its initial biological activity. See col.3, lines 3-7 and col.6, lines 29-32. Peterson does not teach adding a sensitizer to the material prior to

irradiation or a ligand. Peterson also fails to disclose removing residual organic solvent from the biological material.

Horowitz et al, however, teaches a method of sterilizing sensitive biological materials wherein a sensitizer and a stabilizer mixture is preferably added prior to irradiation. See Abstract; col.3, lines 34-39, lines 45-47, lines 60-62. As the sensitizer combined with radiation is disclosed to kill viruses without undue damage to the valuable biological material, it would have been an obvious addition to the method of Peterson. Moreover, Horowitz et al discloses that it was known in the art to combine the treatment of a biological material with irradiation and a stabilizer mixture with a second virucidal treatment such as, treatment with an organic (lipid) solvent. See col.7, line 66 to col.8, line 8. To improve sterilization efficacy, it would have been obvious to employ the virucidal method of Horowitz et al with the irradiation of Peterson.

Wiesehahn et al teaches a method for sterilizing biological materials with UV radiation at a controlled rate and for a time sufficient to sterilize the material. See col.4, lines 20-40. A sensitizer and/or oxygen scavenger may be added to the material before irradiation and preferably the material is irradiated at a temperature below 60 °C, most preferably -10 to 30 °C. A stabilizer (heparin) is added to control any activated clotting factors (col.11, lines 31-33). In order to control any residual clotting factors, it would have been obvious to add heparin in the method of Peterson.

4. Claims 91-94, 260, and 261 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson in view of Horowitz et al and Wiesehahn et al, as applied to claim 85 above, and further in view of Kent (U.S. Patent No. 6,171,549).

With respect to claims 91-94, Peterson teaches irradiation "under standard sterilization conditions...at an intensity and for a time duration sufficient to destroy substantially all of the microorganism contamination" (col.4, lines 59-64). Peterson does not specify what the intensity (dose rate) is. Kent, however, teaches that when sterilizing sensitive biological materials with gamma radiation, one should choose a low dose rate (0.1-3.0 kGy/hr). See Abstract. As this dose rate is disclosed by Kent to be effective in sterilizing without undue damage to the biological material, it would have been obvious to use in Peterson.

As to claims 260 and 261, Peterson does not teach the sterilization of FBS. Kent, however, evidences that it was known in the art at the time of the invention to sterilize FBS using gamma irradiation. See col.13, lines 31-35. As Peterson already teaches the sterilization of blood and blood products, it would have been obvious to use the method of Peterson to sterilize FBS, as well.

5. Claims 85, 86, 95-99, 112, 114, 117, 124, 128, 229, 231, 234, 241-245, 249-251, and 254 are rejected under 35 U.S.C. 103(a) as being unpatentable over Odland (U.S. Patent No. 5,989,498) in view of Wiesehahn et al.

Odland teaches the sterilization of sensitive biological materials (e.g. whole packaged heart valves) at ambient temperature to slightly above ambient (col.4, lines 35-37 and 48-51) with e-beam radiation. Prior to radiation, the biological material is stabilized (cross-linked) with a stabilizer mixture (cross-linking agents) and immersed in a non-aqueous solvent (ethanol) to reduce calcification. See col.7, lines 38-58. The material is then irradiated with e-beam radiation at a dose rate of $2.2 \times 10^4$ kGy/hr (col.3, line 24). Odland further discloses that the biological material may be human, porcine, or bovine. See col.5, lines 28-45. Odland does not

teach that the biological material is equine or the use of sensitizers in the irradiation method. With respect to the sterilization of equine biological material, Odland does discloses that the "term "biological tissue" as used herein refers to a collagen-containing material which may be derived from different animal species, typically mammalian." See col.5, lines 28-30. Therefore, it is deemed obvious to employ the method of Odland to sterilize other types of mammalian tissues, such as equine.

Horowitz et al teaches the sterilization of biological materials, including blood products, wherein the material is treated with a sensitizer and a stabilizer mixture (antioxidant and free-radical scavenger) and subjected to irradiation, where ""irradiation" is to be construed broadly to include any form of radiation conventionally used to inactivate cells...". See col.6, lines 48-50. As the sensitizer combined with radiation is disclosed to kill viruses without undue damage to the valuable biological material, it would have been an obvious addition to the method of Odland.

Wiesehahn et al teaches a method for sterilizing biological materials with radiation wherein a stabilizer (heparin) is added to control any activated clotting factors (col.11, lines 31-33). In order to control any residual clotting factors in the tissue of Odland, it would have been obvious to add heparin.

6. Claims 85, 86, 89, 90, 112-116, 118-123, 125, 229-231, 241, 242, 247, and 254 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horowitz et al in view of Wiesehahn et al.

Horowitz et al teaches a method of radiation sterilizing sensitive human biological materials (cell concentrates, milk, whole blood, etc.) combined with stabilizer mixtures and

sensitizers. See Abstract. The stabilizer can be ascorbate in mixture with another stabilizer. See Table IX. Horowitz et al discloses exposing the materials to particular fluences of radiation (col6, lines 57-62) for particular time periods (col.7, lines 45-48) and the materials may be in a frozen state (col.7, lines 47-48). Radiation sources include UV, gamma, x-rays, and visible light. See col.6, lines 48-56. Moreover, Horowitz et al discloses that it was known in the art to combine the treatment of a biological material with irradiation and a stabilizer mixture with a second virucidal treatment such as, treatment with an organic (lipid) solvent. See col.7, line 66 to col.8, line 8. Horowitz et al does not teach use of a ligand.

Wiesehahn et al teaches a method for sterilizing biological materials with UV radiation at a controlled rate and for a time sufficient to sterilize the material. See col.4, lines 20-40. A sensitizer and/or oxygen scavenger may be added to the material before irradiation and a stabilizer (heparin) is added to control any activated clotting factors (col.11, lines 31-33). In order to control any residual clotting factors, it would have been obvious to add heparin in the method of Horowitz et al.

Although Horowitz et al does not specifically teach the use of polychromatic visible light, infrared, or a combination of visible and UV radiation, it is disclosed that the "term "irradiation" is to be construed broadly to include any form of radiation conventionally used to inactivate cells...either alone or combined with some other agent or condition." See col.6, lines 48-53. Thus, it is deemed obvious to use other known forms of radiation in the method of Horowitz et al.

### *Allowable Subject Matter*

7. Claims 129 and 130 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

8. The following is a statement of reasons for the indication of allowable subject matter: The closest prior art, while teaching irradiation of sensitive biological materials, fails to teach or suggest: a metal ion ligand sensitizer.

9. Claims 131-148 and 204-228 are allowed.

### *New Matter*

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 149-203, 235-240, 252, 253, 255-259, 262, and 263 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Specifically, the specification does not provide sufficient support for the limitation in claims 178 of "said effective rate is not constant and comprises a rate of between about 0.1 kGy/hr to 3.0 kGy/hr for at least a portion of said period of time and a rate of at least 6.0 kGy/hr for at least another portion of said period of time."

Although Applicant points to pages 20-22 of the specification, the Examiner has found no support in these paragraphs. The only teaching these paragraphs give with respect to the dose rate is that preferably the dose rate is constant but when a constant dose rate is impractical or not desired a non-constant dose rate can be used (page 20, fourth paragraph). However, in none of pages 20-22, or elsewhere in the specification, is there guidance as to what different dose rates should be chosen when the dose rate is not constant.

Moreover, although these limitations were allowed in U.S. Patent No. 6,682,695, the Examiner notes that the limitations in questions were present in original claims 1 and 2 of the above patent, and thus had support in the original disclosure.

### *Response to Arguments*

12. Applicant's arguments with respect to the rejected claims have been considered but are moot in view of the new ground(s) of rejection.

### *Conclusion*

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh McKane whose telephone number is 571-272-1275. The examiner can normally be reached on Monday-Wednesday (7:15 am-4:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert J. Warden can be reached on 571-272-1275. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**Leigh McKane**
**Primary Examiner**
**Art Unit 1744**

elm
19 May 2004